PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/404, 31/416, 47/10, 47/12, 47/14, 9/70, A61P 1/08

A1

(11) International Publication Number: WO 00/47208

(43) International Publication Date: 17 August 2000 (17.08.00)

(21) International Application Number: PCT/KR00/00096

(22) International Filing Date: 9 February 2000 (09.02.00)

(30) Priority Data:
1999/4500 9 February 1999 (09.02.99) KR

(71) Applicant (*for all designated States except US*): SAMYANG CORPORATION [KR/KR]; 263, Yonji-dong, Chongno-ku, Seoul 110-470 (KR).

(72) Inventors; and
(75) Inventors/Applicants (*for US only*): SEO, Bo, Youn [KR/KR]; 401-1403 Expo Apt., Chunmin-dong, Yusung-ku, Daejeon 305-390 (KR). CHO, Joong, Woong [KR/KR]; 63-2, Hwaam-dong, Yusung-ku, 305-348 Daejeon (KR). CHOI, Young, Kweon [KR/KR]; 105-1605 Cheonggu Narae Apt., Chunmin-dong, Yusung-ku, Daejeon 305-390 (KR). HWANG, Jun, Seok [KR/KR]; 103-303 Gaenari Apt., Tanbang-dong, Seo-ku, Daejeon 302-223 (KR).

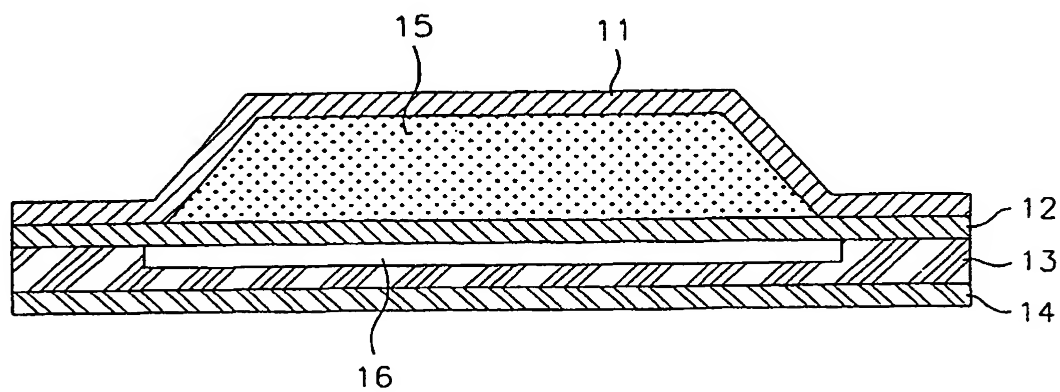
(74) Agent: HUH, Sang, Hoon; Hyecheon Building, 13th floor, 831 Yeoksam-dong, Kangnam-ku, Seoul 135-792 (KR).

(81) Designated States: AU, CA, CH, CN, DE, ES, GB, JP, NZ, SE, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A TRANSDERMAL COMPOSITION OF AN ANTIVOMITING AGENT AND A PREPARATION CONTAINING THE SAME



(57) Abstract

A transdermal composition of the present invention comprises (a) a matrix containing (i) 20 to 80 % by weight of an alcohol, (ii) 1 to 50 % by weight of a skin penetration enhancer selected from the group consisting of a fatty acid and a derivative thereof, a fatty alcohol and a derivative thereof, an amide, a terpene, a surfactant and a mixture thereof, and (iii) 15 to 80 % by weight of water; and (b) 1 to 15 % by weight, based on the weight of the matrix, of an antivomiting agent selected from the group consisting of tropisetron, ondansetron, granisetron and pharmaceutically acceptable salts thereof, which is capable of delivering the antivomiting agent efficiently over a period of a day or more without skin irritation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

A TRANSDERMAL COMPOSITION OF AN ANTIVOMITING AGENT AND A PREPARATION CONTAINING THE SAME

FIELD OF THE INVENTION

The present invention relates to a transdermal composition of an antivomiting agent and a preparation containing the same which is capable of delivering the antivomiting agent efficiently over a period of a day or more without skin irritation.

BACKGROUND OF THE INVENTION

Vomiting is induced by many causes which include pathologic factors, e.g., damaged brain; physiologic factors, e.g., pregnancy; and therapeutic factors, e.g., chemotherapy. The chemotherapy involving the use of an anticancer agent, e.g., cisplatin, causes serious vomiting.

Vomiting is controlled by the emetic center located in cerebral medulla. A vomiting reflex is induced by abnormal activity of the visceral afferent neuron located in the abdominal vagus nerve which receives signals from the chemoreceptor trigger zone(CTZ) located in the emetic center. Thus, the vomiting process is mediated by neurotransmitters such as serotonin(5-hydroxytryptamine sub type 3, 5-HT3), acetylcholine, dopamine and histamine.

Accordingly, neutotransmitter antagonists have been employed as antivomiting agents, and particularly, widely used are serotonin antagonists, e.g., tropisetron, ondansetron, granisetron and dolasetron. Tropisetron, administered parenterally and orally in an amount of 5 mg per a day, is effective in treating acute vomiting caused by cisplatin, and ondansetron is also administered parenterally or orally. Such serotonin antagonists cause no serious

extrapyramidal side effects such as tardive dyskinesia, acute myodystona, akathisia and tremor.

However, the oral administration of an antivomiting agent is not adequate for treating serious vomiting. Intravenous and instillative injection of an antivomiting agent is painful and limited to a hospital practice. Therefore, there has existed a need to develop an improved method for administering antivomiting agents.

A transdermal drug delivery system in general is one of controlled release systems which make it possible to maintain an effective drug concentration in the blood with one application. The transdermal delivery of a drug provides several advantages: it is easy to handle and capable of maintaining an effective drug level in the blood over an extended period; eliminates the fluctuation of the drug concentration in the blood typically seen when a drug is orally administered; is suitable for a drug having a short half-life; avoids initial degradation of a drug in the liver; and is easy to remove after a prescribed time.

However, an effective formulation for transdermal administration of an antivomiting agent has not yet been developed.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a pharmaceutical composition for transdermally administering an antivomiting agent which is capable of delivering the antivomiting agent efficiently to the blood over an extended period without skin irritation.

Another object of the present invention is to provide a preparation containing the pharmaceutical composition.

In accordance with the present invention, there is provided a transdermal

composition comprising (a) a matrix containing (i) 20 to 80 % by weight of a hydrophilic organic solvent, (ii) 1 to 50 % by weight of a skin penetration enhancer selected from the group consisting of a fatty acid and a derivative thereof, a fatty alcohol and a derivative thereof, an amide, a terpene, a surfactant and a mixture thereof, and (iii) 15 to 80 % by weight of water; and (b) 1 to 15 % by weight, based on the weight of the matrix, of an antivomiting agent selected from the group consisting of tropisetron, ondansetron, granisetron and pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

The above objects and features of the present invention will become apparent from the following description of preferred embodiments taken in conjunction with the accompanying drawings, in which:

Fig. 1 shows a schematic representation of the reservoir patch in accordance with one embodiment of the present invention;

Fig. 2 depicts a schematic representation of another reservoir patch in accordance with another embodiment of the present invention; and

Fig. 3 is a schematic representation of the monolithic matrix patch of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

A transdermal composition of the present invention comprises a matrix comprising a hydrophilic organic solvent, a skin penetration enhancer, and water; and an antivomiting agent.

The antivomiting agent which may be used in the present invention is tropisetron, ondansetron, granisetron or a mixture thereof. These antivomiting

agents may be in the form of a free base or a pharmaceutically acceptable salt thereof. The antivomiting agent may be used in an amount ranging from 1 to 15 % by weight, preferably from 3 to 10 % by weight, based on the weight of the matrix.

To deliver an effective amount of an antivomiting agent transdermally, a composition for the transdermal administration has to provide a high skin penetration rate of the antivomiting drug. Formulas (I) to (V), which have been established based on *in vitro* thansdermal delivery data, and various pharmacokinetic parameters (*Drugs, 46,* 925-943 (1993)) are used to define an antivomiting transdermal system, e.g., dose, skin penetration rates and application area;

$$D_t = D_o[1-E] \qquad (I)$$

$$D_{SS} = J_S \cdot A \cdot t \qquad (II)$$

$$K_0 = Cl_T \cdot C_{SS} \qquad (III)$$

$$K_0 = J_S \cdot A \qquad (IV)$$

$$C_{SS} = J_S \cdot A / Cl_T \qquad (V)$$

wherein D_t represents the transdermal administration dose of a drug; D_o, oral administration dose; E is the drug extraction ratio; D_{SS}, the amount of the drug penetrating the skin per unit time; A, the skin area; t, the time for the drug penetrating the skin; J_S, the skin penetration rate of the drug at a steady state; K_0, the infusion rate of the drug; Cl_T, total body clearance; and C_{SS}, the drug level in the blood at a steady state.

According to the above formula and various pharmacokinetic parameters, transdermal penetration rates of 200 to 600 μg/h and 600 to 800 μg/h must be established for tropisetron and ondansetron, respectively, when a plasma

tropisetron level of 3 to 10 ng/ml and a plasma ondansetron level of 10 to 30 ng/ml are to be achieved.

The skin penetration rates of higher than 20 $\mu g/cm^2/h$ is a prerequisite to provide the patch area of lower than 40 cm^2 for patient's convenience. Because the higher the rate of an antivomition agent is, the less the patch area required to deliver an effective amount of an antivomiting agent is.

However, the actual skin penetration rate of an antivomiting agent is very low due to the resistance of the lipophilic outmost layer(keratotic layer) of the skin toward drug penetration.

Accordingly, the skin penetration rate of an antivomiting agent is enhanced by way of using a skin penetration enhancer. The skin penetration enhancer reduces the diffusional resistance of the skin and promotes the distribution of the drug into the lipophilic part of the skin by modifying the physicochemical properties of the keratotic layer.

The skin penetration enhancers which may be used in the present invention include a fatty acid and a derivative thereof, a fatty alcohol and a derivative thereof, an amide, a terpene, a sulfactant and a mixture thereof.

Both the fatty acid and fatty alcohol disrupt the bilayer structure of the keratotic layer to enhance intercellular fluidity, thereby enhancing the skin penetration rate of an antivomiting agent.

Representative fatty acids include C_{10-18} saturated or unsaturated fatty acids such as capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid and linolenic acid. Among these, lauric acid and oleic acid are preferred and oleic acid is more preferred.

Examples of the fatty acid derivative include fatty acid esters. Representative fatty acid esters include glycerol monolaurate, glycerol monooleate,

glycerol monolinoleate, glycerol trilaurate, glycerol trioleate, glycerol tricaprylate, propylene monolaurate, propylene glycol dilaurate, caprylic/capric triglyceride, methyl laurate, methyl caprate, isopropyl myristate, isopropyl palmitate, ethyl oleate, oleyl oleate. Among these, glycerol monolaurate and propylene glycol monolaurate are preferred and glycerol monolaurate is more preferred.

Representative fatty alcohols include $C_{8\text{-}18}$ alcohols such as *n*-octanol, *n*-nonanol, decanol, lauryl alcohol, oleyl alcohol and linoleyl alcohol, and among these, *n*-nonanol and lauryl alcohol are preferred.

Fatty alcohol derivatives include fatty alcohol ethers and representative examples are polyoxyethylene lauryl ether, polyoxylethylene cetyl ether, polyoxyethylene stearyl ether and polyoxyethylene oleyl ether.

Each of the fatty acid and fatty alcohol, when combined with propylene glycol, synergistically promotes the skin penetration of an antivomiting agent.

Representative amides include N,N-diethyl-m-toluamide, lauramide diethanolamine, urea, dimethylformamide and dimethylacetamide. Among these, N,N-diethyl-m-toluamide, lauramide diethanolamine and urea are preferred and N,N-diethyl-m-toluamide is more preferred. The amide increases the solubility of a drug in the keratotic layer and promotes the distribution of the drug into the skin. Particularly, 1 to 10 % by weight, preferably 1 to 5 % by weight, of N,N-diethyl-m-toluamide, when combined with 1 to 5 % by weight of glycerol monolaurate, synergistically promotes the skin penetration of an antivomiting agent.

The inventive composition may further comprise a terpene. Representative terpenes include *l*-menthol, menthone, *d*-limonene, 1,8-cineol, nerolidol, carveol and camphor. Among these, *l*-menthol, *d*-limonene and nerolidol are preferred and *l*-menthol is more preferred. The terpene, when combined with ethanol, synergistically promotes the skin penetration of an

antivomiting agent by enhancing the distribution of the drug into the keratotic layer.

The inventive composition may still further comprise a nonionic surfactant. Representative nonionic surfactants that can be used in the present invention include polyoxyethylene-9-nonylphenyl ether, polyethylene glycol-40 hydrogenated castor oil, polyethylene glycol-35 castor oil and octoxynol-11. Preferred, among these, are polyoxyethylene (n=10) oleyl ether, polyoxyethylene-9-nonylphenyl ether, polyethylene glycol-40 hydrogenated castor oil RH40 and octoxynol-11, and more preferred are polyoxyethylene (n=10) oleyl ether and polyethylene glycol-40 hydrogenated castor oil RH40, polyoxyethylene sorbitan monolauryl ester, polyoxyethylene sorbitan trilauryl ester, polyoxyethylene sorbitan palmityl ester, polyoxyethylene sorbitan stearyl ester, polyoxyethylene sorbitan oleyl ester(Tween^R, ICI), sorbitan monolauryl, sorbitan monopalmityl and sorbitan monostearyl esters(Span^R, ICI). The nonionic surfactant promotes the skin penetration of a drug with a less damage to the skin than an ionic surfactant, i.e., an anionic, cationic or amphoteric surfactant(Water, K.A., *Penetration enhancers and their use in transdermal therapeutic system, Transdermal Drug Delivery*, 212-224, Dekker, (1989); and Eagle et al., *J. Toxicol. cut and Ocular toxicol, 11*, 77-92 (1992)).

The skin penetration enhancer may be used in an amount ranging from 1 to 50 % by weight, preferably from 1 to 10 % by weight, based on the weight of the matrix.

The hydrophilic organic solvent which may be used in the present invention is a low molecular weight alcohol such as ethanol, isopropanol, butanol, benzyl alcohol, propylene glycol, glycerin, polyethylene glycol having a molecular weight of 600 or less, diethylene glycol monoethyl ether, triacetin, N-methylpyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, decylmethyl sulfoxide,

dioxane, lactone and a mixture thereof. Among these, preferred are a mixture of ethanol and propylene glycol, a mixture of ethanol and glycerin, and a mixture of ethanol and diethylene glycol monoethyl ether and more preferred is a mixture of ethanol and propylene glycol. The hydrophilic organic solvent may be used in an amount ranging from 20 to 80 % by weight, preferably from 20 to 50 % by weight, based on the weight of the matrix. The use of a mixture of 10 to 30 % by weight of ethanol and 10 to 50 % by weight of propylene glycol based on the weight of the matrix is still more preferred.

Ethanol reversibly changes the structure of the keratotic layer by extracting polar lipids therefrom, thereby promoting the skin penetration of an antivomiting agent, and also plays the role of enhancing the solubilization of the antivomiting agent and another watersoluble components of the matrix.

Propylene glycol, when combined with a fatty acid or a terpene, synergically promotes the skin penetration of an antivomiting agent.

The transdermal matrix in the present invention contains 15 to 80 % by weight of water which is distilled water or pH buffer solution.

The composition of the present invention may further comprise a thickener. Representative thickeners include polyvinylpyrrolidone, colloidal silicon dioxide, polyvinyl alcohol, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbopol and polyoxyethylene-polyoxypropylene block copolymer(poloxamerR, BASF), and preferred is hydroxypropylcellulose. The thickener may be used in an amount ranging from 1 to 10 % by weight based on the weight of the matrix.

The composition of the present invention may be formulated into a preparation for the transdermal administration, e.g., a patch. Examples of the patch which may be used in the present invention include a reservoir patch and a

monolithic matrix patch.

An adhesive matrix patch, another form of patch, may not be suitably employed in the present invention because it can carry only limited amounts of an antivomiting agent and a soluble skin penetration enhancer in its adhesive layer.

The reservoir patch which may be used in the present invention is composed of an impervious protective layer, a reservoir layer containing the composition of the present invention, a drug-permeable membrane, an adhesive layer, a release strip and optionally a peelable disc. The reservoir layer is positioned between the impervious protective layer and one surface of the drug-permeable membrane. The whole surface or an edge portion of one side of adhesive layer is attached to the other surface of the drug-permeable membrane; and optionally the central portion thereof is attached to the peelable disc. The other side of the adhesive layer is attached to the release strip. The peelable disc and the release strip are removed before use.

Fig. 1 shows an embodiment of the reservoir patch of the present invention, which comprises a reservoir layer(15) containing the inventive composition arranged between an impervious protective layer(11) and a drug-permeable membrane(12), an adhesive layer(13) attached to the bottom surface of the drug-permeable membrane(12) at the edge and to a peelable disc(16) at its central portion, and a release strip(14) attached to the other side of the adhesive layer.

Fig. 2 shows another embodiment of the reservoir patch of the present invention, which comprises a reservoir layer(25) containing the inventive composition positioned between an impervious protective layer(21) and a drug-permeable membrane(22), an adhesive layer(23) attached to the bottom surface of the drug-permeable membrane and a release strip(24) attached to the other side of the adhesive layer.

The impervious protective layer provides the seal to protect the patch form losing volatile component of the composition and it may be made of a polyester, polyethylene or polypropylene. The drug-permeable membrane provides a physical backing of the reservoir layer, which may be porous or nonporous. The drug-permeable membrane may be made of polyethylene or polypropylene and the nonporous membrane may be a film made of ethylenevinyl acetate, silicon rubber or polyolefin. The drug-permeable membrane may be selected to control the release rate of the drug in the composition.

The protective layer and the drug-permeable membrane are sealed by heating the edge portion, thereby enclosing the reservoir layer. The adhesive layer may be made of polyisobutylene, acrylate or silicon.

Fig.3 shows an embodiment of the monolithic matrix patch of the present invention, which comprises an impervious protective layer(31), a reservoir layer(35), an adhesive layer(33) and a release strip(34). The reservoir layer(35) is positioned between the impervious protective layer(31) and the adhesive layer(33) which is attached to the release strip(34). The reservoir layer(35) contains the inventive composition dispersed in a polymer, e.g., polyvinylpyrrolidone, polyvinyl alcohol and hydroxyethylcellulose. The reservoir layer may be a hydrogel that comprises 30 to 60 % by weight of water, 25 to 50 % by weight of a composition for the transdermal administration, and 5 to 20 % by weight of a polymer, based on the weight of the reservoir layer.

The patch of the present invention may be prepared by dispersing the inventive composition for the transdermal administration in a polymer solution.

The composition and preparation of the present invention release an antivomiting agent at a rate sufficient for maintaining an effective level of the drug in the blood over a period of 24 to 72 hours at a skin contact area of 10 to 40 cm^2.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Further, percentages given below for solid in solid mixture, liquid in liquid, and solid in liquid are on a wt/wt, vol/vol and wt/vol basis, respectively, and all the reactions were carried out at room temperature, unless specifically indicated otherwise.

Reference Example: Determination of Skin Penetration Rate

The skin penetration rate of a drug was determined using a Franz diffusion cell(Model FDC-400, Crown Glass Co., USA) as follows:

A piece of cadaver skin was placed between the donor and receptor compartments of the Franz diffusion cell such that the keratotic layer of the skin faced the donor compartment. The effective area of the skin exposed to the receptor solution was 0.636 cm^2. The receptor compartment was filled with 5 ml of distilled water(receptor solution), and stirred at 600 rpm using a magnetic bar while maintaining the temperature at 32±0.5℃ using a thermostat with a circulatory pump. The donor compartment was filled with a degassed transdermal composition and then sealed. The amount of the drug in the receptor compartment was adjusted such that the drug concentration in the receptor solution does not exceed 10 % of the maximum solubility of the drug during the course of the experiment. Samples of the receptor solution was taken at 2, 4, 5, 12, 20 and 24 hours.

The skin penetration rate was determined by the amount of the drug penetrated per unit area of the skin per unit time, according to formula (VI):

$$Js = \frac{1}{A}\left(\frac{dQ}{dt}\right)ss \qquad \text{(VI)}$$

wherein Js and A have the same meanings as defined previously; and (dQ/dt)ss is the amount of the drug penetrated per unit time at a steady state.

Example 1: Preparation of Transdermal Composition

30 % by weight of ethanol, 27 % by weight of propylene glycol, 3 % by weight of oleic acid, and 40 % by weight of water were mixed and then 3 % by weight of ondansetron was added thereto to obtain a transdermal composition(Composition 1).

The procedure of Reference Example was used to determine that the skin penetration rate of ondansetron was 71.4 μg/cm²/h.

Comparative Example 1: Preparation of Comparative Composition

3 % by weight of ondansetron was dissolved in 100 % by weight of water to obtain a comparative composition(Comparative Composition 1). This composition showed no significant penetration of ondansetron through the skin.

Comparative Example 2: Preparation of Comparative Composition

3 % by weight of ondansetron was added to a mixture of 20 % by weight of ethanol and 80 % by weight of water to obtain a comparative composition(Comparative Composition 2). The skin penetration rate of ondansetron was 0.7 μg/cm²/h.

Comparative Example 3: Preparation of Comparative Composition

3 % by weight of ondansetron was added to a mixture of 20 % by weight of

ethanol, 20 % by weight of propylene glycol and 60 % by weight of water to obtain a comparative composition(Comparative Composition 3). The skin penetration rate of ondansetron was 1.0 μg/cm²/h.

Comparative Example 4: Preparation of Comparative Composition

3 % by weight of ondansetron was added to a mixture of 40 % by weight of ethanol and 60 % by weight of propylene glycol to obtain a comparative composition (Comparative Composition 4). The skin penetration rate of ondansetron was 1.7 μg/cm²/h.

Comparative Example 5: Preparation of Comparative Composition

3 % by weight of ondansetron was added to a mixture of 20 % by weight of ethanol, 5 % by weight of N-methylpyrrolidone and 75 % by weight of water to obtain a comparative composition (Comparative Composition 5). The skin penetration rate of ondansetron was 3.1 μg/cm²/h.

Comparative Example 6: Preparation of Comparative Composition

3 % by weight of ondansetron was added to a mixture of 40 % by weight of ethanol and 60 % by weight of diethylene glycol monoethyl ether to obtain a comparative composition (Comparative Composition 6). The skin penetration rate of ondansetron was 1.4 μg/cm²/h.

As can be seen from the results of Example 1 and Comparative Examples 1 to 6, Composition 1 with the skin penetration enhancer exhibits a higher skin penetration rate of ondansetron than Comparative Compositions 1 to 7 without the skin penetration enhancer.

Example 2: Preparation of Transdermal Composition

Added to an aqueous solution containing 20 % by weight of ethanol, 15 % by weight of propylene glycol, 3 % by weight of glycerol monoleate, 2 % by weight of polyoxyethylene(n=10) oleayl ether, and 60 % by weight of water was tropisetron to a concentration of 5 % by weight to obtain a transdermal composition(Composition 2). The skin penetration rate of tropisetron was 30.8 $\mu g/cm^2/h$.

Examples 3 to 42: Preparation of Transdermal Composition

Transdermal compositions(Compositions 3 to 42) were obtained by repeating the procedure of Example 1 or 2 using the ingredients shown in Table 1 and the skin penetration rate of the active ingredient in each of the compositions was determined by the procedure of Reference Example.

Table 1

Composition No.		3	4	5	6	7	8	9	10	11	12
Antivomiting agent*	Tropisetron										
	Ondansetron	3	3	3	3	3	3	3	3	3	3
Ingredient (parts by weight)	Ethanol	20	20	20	20	20	20	20	20	20	20
	Propylene Glycol	50	50	50	30	38	38	15		15	29
	Glycerin										
	Diethylene Glycol Monoethyl Ether										
	Polyethylene Glycol-400								15		
	Lauric Acid								1		
	Oleic Acid	3	5	10	1	3	3				
	Octanol										
	n-Nonanol					4					
	Glycerol Monolaurate										
	Propylene Glycol Monolaurate							5	5	5	15
	N,N-Diethyl-m-toluamide										
	l-Methol									1	1
	d-Limonene										
	l-Lactic Acid										
	Polyoxyethylene(n=10) Oleyl Ether										
	Polyethylene Glycol-40 Hydrogenated Castor Oil				5			10	10	10	
	Octoxynol-11					5	5				5
	Water	27	25	20	44	30	34	50	49	49	30
Skin Penetration Rate (μg/cm²/h)		30.7	32.2	31.8	30.4	85.8	75.7	26.6	35.3	30.8	47.1

Table 1 (Continued)

Composition No.		13	14	15	16	17	18	19	20	21	22
Antivomiting agent*	Tropisetron										
	Ondansetron	3	3	3	3	3	6	6	6	6	6
Ingredient (parts by weight)	Ethanol	20	20	20	20	20	20	20	20	20	20
	Propylene Glycol	25		10	25	40	15	15	15	15	15
	Glycerin	13									
	Diethylene Glycol Monoethyl Ether										
	Polyethylene Glycol-400										
	Lauric Acid										
	Oleic Acid	3									
	Octanol	1									
	n-Nonanol		3								
	Glycerol Monolaurate			3	3	3	1	3	5	3	3
	Propylene Glycol Monolaurate									0.5	
	N,N-Diethyl-m-toluamide										
	l-Methol										
	d-Limonene										0.5
	l-Lactic Acid										
	Polyoxyethylene(n=10) Oleyl Ether		2	2	2	2	3	3	3	2	2
	Polyethylene Glycol-40 Hydrogenated Castor Oil	5									
	Octoxynol-11										5
	Water	33	75	65	50	35	61	59	57	59.5	59.5
Skin Penetration Rate (μg/cm²/h)		36.6	48.3	35.1	25.7	26.9	37.4	43.6	50.2	62.6	87.1

Table 1 (Continued)

Composition No.		23	24	25	26	27	28	29	30	31	32
Antivomiting agent*	Tropisetron										
	Ondansetron	6	6	6	6	6	6	6	6	6	6
Ingredient (parts by weight)	Ethanol	20	20	20	20	20	20	20	20	20	20
	Propylene Glycol	15	15	15	15	15	15	15	15	15	15
	Glycerin										
	Diethylene Glycol Monoethyl Ether										
	Polyethylene Glycol-400										
	Lauric Acid										
	Oleic Acid	0.5									
	Octanol										
	n-Nonanol										
	Glycerol Monolaurate	3	3	1	1	1	1	2		1	1
	Propylene Glycol Monolaurate		0.5								
	N,N-Diethyl-m-toluamide			1	3	5	10	3	3	3	3
	l-Methol										
	d-Limonene		1								
	l-Lactic Acid									0.3	0.5
	Polyoxyethylene(n=10) Oleyl Ether	2	2								
	Polyethylene Glycol-40 Hydrogenated Castor Oil										
	Octoxynol-11										
	Water	59.5	58.5	63	61	59	54	60	62	60.7	60.5
Skin Penetration Rate (μg/cm²/h)		47.1	95.8	79.2	81.4	115.3	33.2	144.1	23.2	102.6	208.8

Table 1 (Continued)

Composition No.		33	34	35	36	37	38	39	40	41	42
Antivomiting agent*	Tropisetron		5	5	5	5	5	6	6	6	6
	Ondansetron	6									
Ingredient (parts by weight)	Ethanol	20	20	20	20	20	20	20	20	20	20
	Propylene Glycol	15	15	15	15	15	15		15		15
	Glycerin							15	5		
	Diethylene Glycol MonoethylEther									40	
	Polyethylene Glycol-400										
	Lauric Acid										
	Oleic Acid										
	Octanol				1						
	n-Nonanol										
	Glycerol Monolaurate	1	3		3	1	1	1	1		3
	Propylene Glycol Monolaurate			3						20	
	N,N-Diethyl-m-toluamide	3				1	2	2	2		
	l-Methol										
	d-Limonene	1									1
	l-Lactic Acid										
	Polyoxyethylene(n=10) Oleyl Ether		2	4	5						2
	Polyethylene Glycol-40 Hydrogenated Castor Oil										
	Octoxynol-11										
	Water	60	60	58	56	63	62	62	57	10	59
Skin Penetration Rate (μg/cm²/h)		55.4	30.8	39.4	42.7	69.1	85.4	64.8	67.9	49.1	33.7

Antivomiting agent* : parts by weight, based on the weight of the matrix.

Formulation Example 1: Reservoir Patch

A polyester film(Scotchpak 1022, 3M, USA) was coated with an acrylate adhesive(Durotak 87-2196, National Starch) in a thickness of 500 μm, and the resulting film was dried at room temperature for 30 min. and further dried at 100℃ for 15 min. A peelable disc(RayopeelTM, LR4/25, ucb Transpac N.V.) was laminated thereon to obtain an adhesive film.

20 % by weight of ethanol, 15 % by weight of propylene glycol, 1 % by weight of glycerol monooleate, 2 % by weight of N,N-diethyl-m-toluamide and 62 % by weight of water were mixed to obtain a matrix solution. 4.5 % by weight of hydroxypropylcellulose was added to the matrix solution and 6 % by weight of tropisetron was added thereto to obtain a gel.

The gel was placed on a protective film(Scotchpak 1012, polyester film, 3M) in an amount of 150 mg/cm^2 and then a drug-permeable membrane(Cotran, microporous polyethylene film, 3M) was placed thereon. The edge portion of the reservoir layer was sealed by heating. The peripheral portion of the drug-permeable membrane was then fixed on the adhesive film and cut in a desired shape to obtain a reservoir patch.

The skin penetration rate of tropisetron from this reservoir patch was 47.2 $\mu g/cm^2/h$.

Formulation Example 2: Monolithic Matrix Patch

20 % by weight of ethanol, 15 % by weight of polyproylene glycol, 2 % by weight of oleic acid, 3 % by weight of octanol, 5 % by weight of octoxynol and 55 % by weight of water were mixed, and added thereto were 8 % by weight of

polyvinylpyrrolidone and 4 % by weight of polyvinyl alcohol dissolved in an distilled water. The resulting solution was stirred vigorously to make it homogeneous. 4 % by weight of hydroxylethylcellulose and 6 % by weight of tropisetron were added thereto and the resultant was homogenized.

The solution thus obtained was placed in a mould to a depth of 2 mm and kept at 4 ℃ for a day to obtain a hydrogel.

The hydrogel was laminated on an impervious protective layer precoated with an acrylate adhesive(Durotak 87-2196, National Starch) and then a release strip coated with silicon was attached thereon to obtain a monolithic matrix patch.

The skin penetration rate of tropisetron from the monolithic matrix was 21.3 ㎍/㎠/h.

Test Example

The reservoir patch obtained in Formulation Example 1 was attached to the skin of each of 10 adult subjects for the duration of 24 hours and then dermal irritations such as erythema, edema, itchness and pain were examined and evaluated the degree of irritation by the scale of 0(no irritation) to 4(strong irritation). The test result showed only minor degrees of skin irritation: erythema, 0.3; edema, 0.2; itchness, 0; and pain 0.1.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

CLAIMS

What is claimed is:

1. A transdermal composition comprising (a) a matrix containing (i) 20 to 80 % by weight of a hydrophilic organic solvent, (ii) 1 to 50 % by weight of a skin penetration enhancer selected from the group consisting of a fatty acid and a derivative thereof, a fatty alcohol and a derivative thereof, an amide, a terpene, a surfactant and a mixture thereof, and (iii) 15 to 80 % by weight of water; and (b) 1 to 15 % by weight, based on the weight of the matrix, of an antivomiting agent selected from the group consisting of tropisetron, ondansetron, granisetron and pharmaceutically acceptable salts thereof.

2. The transdermal composition of claim 1, wherein the hydrophilic organic solvent is selected from the group consisting of ethanol, isopropanol, butanol, benzyl alcohol, propylene glycol, glycerin, polyethylene glycol having a molecular weight of 600 or less, diethylene glycol monoethyl ether, triacetin, N-methylpyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, decylmethyl sulfoxide, dioxane, lactone and a mixture thereof.

3. The transdermal composition of claim 2, wherein the hydrophilic organic solvent is a mixture of ethanol and propylene glycol.

4. The transdermal composition of claim 3, wherein the mixture consists of 10 to 30 % by weight of ethanol and 10 to 50 % by weight of propylene glycol.

5. The transdermal composition of claim 1, wherein the fatty acid is selected from the group consisting of capric acid, lauric acid, myristic acid, palmitic acid, stearic

acid, oleic acid, linoleic acid and linolenic acid.

6. The transdermal composition of claim 5, wherein the fatty acid is oleic acid used in an amount of 1 to 10 % by weight based on the weight of the matrix.

7. The transdermal composition of claim 1, wherein the fatty acid derivative is a fatty acid ester.

8. The transdermal composition of claim 7, wherein the fatty acid ester is selected from the group consisting of glycerol monolaurate, glycerol monooleate, glycerol monolinoleate, glycerol trilaurate, glycerol trioleate, glycerol tricaprylate, propylene monolaurate, propylene glycol dilaurate, caprylic/capric triglyceride, methyl laurate, methyl caprate, isopropyl myristate, isopropyl palmitate, ethyl oleate, oleyl oleate.

9. The transdermal composition of claim 8, wherein the fatty acid ester is glycerol monolaurate used in an amount of 1 to 5 % by weight based on the weight of the matrix.

10. The transdermal composition of claim 1, wherein the fatty alcohol is selected from the group consisting of *n*-octanol, *n*-nonanol, decanol, lauryl alcohol, oleyl alcohol and linoleyl alcohol.

11. The transdermal composition of claim 1, wherein the fatty alcohol derivative is an ether thereof.

12. The transdermal composition of claim 11, wherein the fatty alcohol ether is selected from the group consisting of polyoxyethylene lauryl ether, polyoxylethylene cetyl ether, polyoxyethylene stearyl ether and polyoxyethylene oleyl ether.

13. The transdermal composition of claim 1, wherein the amide is selected from the group consisting of N,N-diethyl-m-toluamide, lauramide diethanolamine, urea, dimethylformamide and dimethylacetamide.

14. The transdermal composition of claim 13, wherein the amide is N,N-diethyl-m-toluamide used in an amount of 1 to 10 % by weight based on the weight of the matrix.

15. The transdermal composition of claim 1, further comprising a terpene selected from the group consisting of *l*-menthol, menthone, *d*-limonene, 1,8-cineol, nerolidol, carveol and camphor.

16. The transdermal composition of claim 1, further comprising a nonioinic surfactant selected from the group consisting of polyoxyethylene-9-nonylphenyl ether, polyethylene glycol-40 hydrogenated castor oil, polyethylene glycol-35 castor oil and octoxynol-11, polyoxyethylene stearate, polyoxyethylene sorbitan monolauryl ester, polyoxyethylene sorbitan trilauryl ester, polyoxyethylene sorbitan palmityl ester, polyoxyethylene sorbitan stearyl ester, polyoxyethylene sorbitan oleyl ester, sorbitan monolauryl ester, sorbitan monopalmityl ester and sorbitan monostearyl ester.

17. The transdermal composition of claim 1, wherein water is distilled water or pH buffer solution.

18. The transdermal composition of claim 1, further comprising a thickener.

19. The transdermal composition of claim 18, wherein the thickener is selected from the group consisting of polyvinylpyrrolidone, colloidal silicon dioxide, polyvinyl alcohol, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carbopol and polyoxyethylene polyoxypropylene block copolymer.

20. A preparation comprising the transdermal composition according to any one of claims 1 to 19.

21. The preparation of claim 20, which is a reservoir patch or a monolithic matrix patch.

22. The preparation of claim 21, wherein the reservoir patch is composed of a reservoir layer containing the transdermal composition, an impervious protective layer, a drug-permeable membrane, an adhesive layer and release strip, the reservoir layer being positioned between the protective layer and one surface of the drug-permeable membrane, and the adhesive layer, between the other surface of the drug-permeable membrane and the release strip.

23. The preparation of claim 21, wherein the monolithic matrix patch is composed of a reservoir layer containing the transdermal composition, an

impervious protective layer, an adhesive layer, and a release strip, the reservoir layer being positioned between the protective layer and one surface of the adhesive layer, and the release strip being attached to the other surface of the adhesive layer.

FIG.1

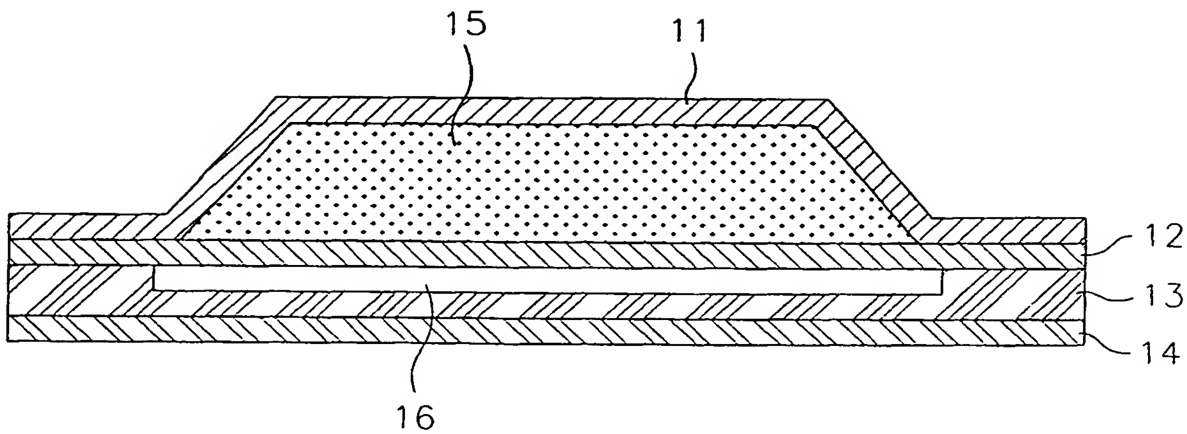


FIG.2

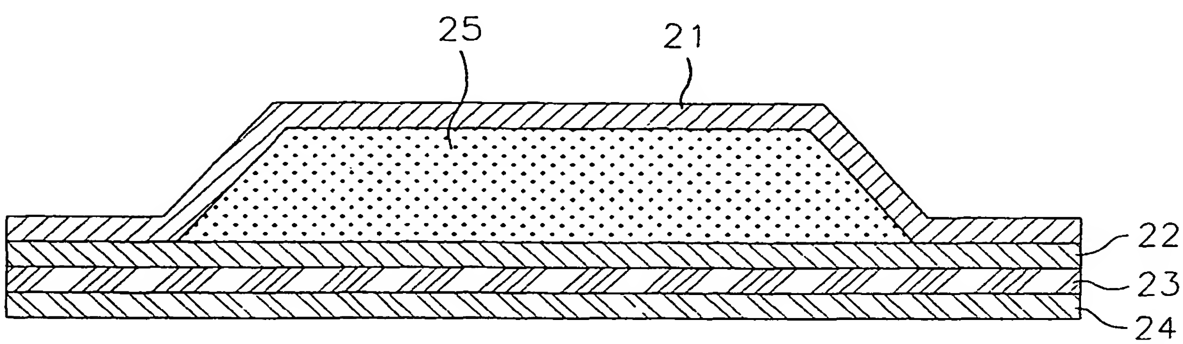
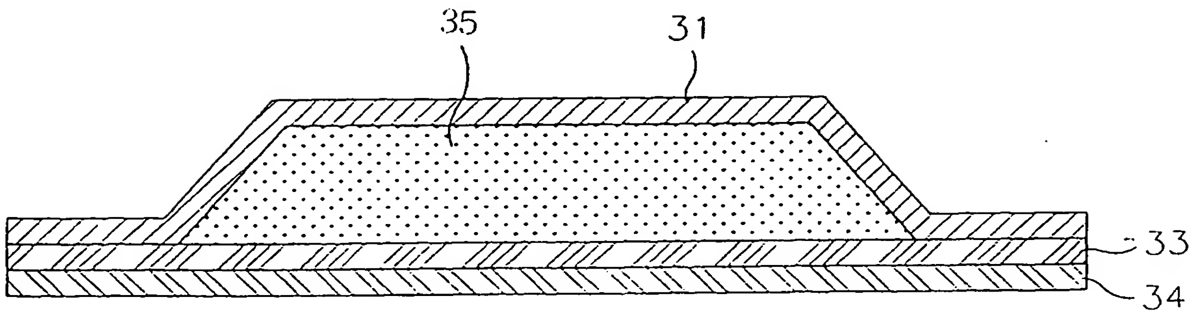


FIG.3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 00/00096

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: A 61 K 31/404, 31/416, 47/10, 47/12, 47/14, 9/70; A 61 P 1/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: A 61 K, A 61 P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/30244 A1 (MINNESOTA MINING AND MANUFACTURING COMPANY) 16 July 1998 (16.07.98), totality.	1-23
X	EP 0682942 A1 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 22 November 1995 (22.11.95), abstract; page 3, line 9-page 4, line 39; page 5, line 56-page 6, line 3; example 15; claims.	1,2,7-9,11,12, 15-21
A	WO 98/53815 A1 (EFFING, JOCHEM) 03 December 1998 (03.12.98), abstract, claims.	1-23
P,A	US 5908619 A (SCHOLZ) 01 June 1999 (01.06.99), abstract; claims.	1-23

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 April 2000 (25.04.00)	12 July 2000 (12.07.00)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Krenn Telephone No. 1/53424/435

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/FR 00/00096

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO A1 9830244	16-07-1998	AU A1 57098/98	03-08-1998
		EP A1 957939	24-11-1999
		US A 6019997	01-02-2000
EP A1 682942	22-11-1995	AU A1 58656/94	15-08-1994
EP A4 682942	04-12-1996	CA AA 2153882	04-08-1994
		WO A1 9416682	04-08-1994
WO A1 9853815	03-12-1998	AU A1 31706/97	30-12-1998
US A 5908619	01-06-1999	AU A1 53858/98	03-08-1998
		EP A1 963157	15-12-1999
		WO A1 9830096	16-07-1998